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124. (New) The method of Claim ~~123~~ wherein the anti-TNF chimeric antibody is cA2.

REMARKS

Claim Amendments

Claim 108 has been cancelled. Claims 106, 110, 111 and 112 have been amended to reduce issues and exclude the treatment of disease resulting from infection. Support for the amended claims is found, for example, in the Specification on page 61, line 14 to page 63, line 29. These amendments have been presented in an effort to advance prosecution. Claims 113-124 have been added. Claims 113-118, 120 and 122 recite methods of treating TNFα-mediated disease, other than disease resulting from infection, by administering an anti-TNF chimeric antibody comprising an IgG1 constant region. Support for these claims is found in the Specification on page 33, lines 2-11 and page 36, lines 15-24. Claims 119-122 recite methods of treatment wherein the non-human variable region of the administered antibody comprises an amino acid sequence of SEQ ID NO.: 3 or SEQ ID NO.: 5 (Claims 119-120) or comprises a polypeptide encoded by SEQ ID NO.: 2 or SEQ ID NO.: 4 (Claims 121-122). Support for these claims is found in the Specification on page 12, lines 19-24 and Figures 16A and 16B. Claims 123 and 124 recite methods of treating a TNFα-mediated diseases selected from a recited group of diseases, comprising administering an anti-TNF chimeric antibody that competitively inhibits binding of TNF to cA2 (Claim 123) and administering an anti-TNF chimeric antibody that is cA2 (Claim 124). Support for these claims is found in the Specification at page 61, line 14 to page 63, line 25. No new matter has been added.

Specification Amendments

Amendments to the Specification have been made to correct informalities and to renumber the Figures in the Specification to match the formal drawings. These amendments are necessary because two photographs, original Figures 16 and 32, have been deleted. The original photographs are unavailable and not necessary for an understanding of the invention. No new matter has been added.

Information Disclosure Statement

Page 2 of the Final Office Action states that a copy of the 1449 form dated February 4, 1994 was provided with the Office Action. However, although the filing date of this application is February 4, 1994, the dates of the 1449 forms for the Information Disclosure Statement (IDS) and the Supplemental IDS for this application are January 26, 1995, and August 4, 1995, respectively. The Examiner has provided an initialed and dated copy of the 1449 form for the January 26, 1995 IDS. Applicants hereby request an initialed and dated copy of the 1449 form for the August 4, 1995 Supplemental IDS. An extra copy of the original form is enclosed herewith for the Examiner's convenience. If additional copies of the references are also required, the Examiner is urged to telephone the undersigned and hand delivery of the references will be arranged.

Priority

The Examiner believes that the claimed invention does not have priority to the earlier applications because the claims are not enabled under 35 U.S.C. § 112, first paragraph. Applicants disagree. The priority applications to this application contain substantially identical specifications to the specification in this application in terms of enabling the claims. Therefore,

since the amendments and arguments in this Response establish that the present specification enables the original and amended claims, the prior applications likewise enable the claims. Accordingly, Applicants request acknowledgment that the present claims are entitled to the earliest claimed priority date.

Objection to the Specification and Rejection of Claim 110 Under 35 U.S.C. § 112, First Paragraph

The objection to the Specification and rejection of Claim 110 under 35 U.S.C. § 112, first paragraph, as set forth in the previous Office Action, are maintained. The Examiner stated:

> "the nucleic acid and amino acid sequences shown in Figure 17B, which correspond to SEQ ID NO.: 4 and 5 are identified in the Brief Description of the Drawings as corresponding to constant region sequences of cA2. The sequence of the heavy chain variable region of the cA2 monoclonal antibody is not disclosed. It is unclear that one of skill in the art could derive a monoclonal antibody identical to the cA2 antibody claimed based on the description in the specification."

Applicants have amended an inadvertent error in the Specification to clarify that Figure 17B (renumbered Figure 16B after amendment) is a nucleic acid sequence (SEQ ID NO.: 4) and corresponding amino acid sequence (SEQ ID NO.: 5) of the heavy chain variable region of the cA2 monoclonal antibody. Since the sequence of the heavy chain variable region of the cA2 monoclonal antibody is disclosed, the claimed invention is enabled by the Specification and a deposit is not required.

Withdrawal of the objection to the Specification and withdrawal of the rejection of Claim 110 are respectfully requested.

Objection to the Specification and Rejection of Claims 106-112 Under 35 U.S.C § 112, First Paragraph

The Specification is objected to and Claims 106-112 are rejected under 35 U.S.C. § 112, first paragraph for failing to provide an enabling disclosure for the scope of the TNFα-mediated diseases encompassed by the claims.

The Examiner believes that the state of the art was unpredictable, at the time the invention was made, with regard to the production and administration of anti-TNFα antibodies for treatment of sepsis and septic shock. He states that Natanson et al. reports that the administration of cytokine-suppressing agents was ineffective in treating sepsis, and that administration of a TNF antagonist may be harmful. Furthermore, the Examiner believes that the Specification does not teach identification of patients who would benefit from such treatment nor the timing, duration and delivery of the antibody that would benefit a patient without producing harm.

Applicants believe that the Specification is sufficient to enable the originally presented claims. However, to speed prosecution, Applicants have amended Claims 106 and 110-112 to remove reference to treatment of TNFα-mediated disease resulting from infection. Dependent Claims 107 and 109 carry the limitations of Claim 106, from which they depend.

Accordingly, withdrawal of the rejection of Claims 106-112 and withdrawal of the objection to the Specification are respectfully requested.

Rejection of Claims 106-112 Under 35 U.S.C. § 103

Claims 106-112 are rejected under 35 U.S.C. § 103 as being unpatentable over Shalaby et al. (U) or Brennan et al. (V) or Buurman (U.S. Patent No. 5,183,657) in view of Möller et al. (U.S. Patent No. 5,231,024 or Cytokine, 2(3):162-169 (1990) or Rathjen et al. (WO 91/02078) and Morrison (Science, 1985,

225:1202-1207).

Obviousness under 35 U.S.C. § 103 is a question of law based on the factual inquiries set forth in Graham v. John Deere Co., 383 U.S. 1, 17, 148 U.S.P.Q. 459, 467 (1966):

> Under 103, the scope and content of the prior art are to be determined; differences between the pertinent art and the claims at issue are to be ascertained; and the level of ordinary skill in the prior art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the origin of the subject matter sought to be patented. As indicia of obviousness or nonobviousness, these inquiries may have relevancy. (citation omitted)

The scope and content of the prior art, differences between the prior art and the claims at issue, and the level of ordinary skill in the pertinent art all indicate that Applicants' invention is not obvious.

Applicants' invention is drawn to methods of treating TNFα-mediated disease, other than disease caused by infection, in a human comprising administering TNF-inhibiting amounts of an anti-TNF chimeric antibody. Preferred claimed methods are directed to administering cA2; antibodies which competitively inhibit binding of TNF to cA2; antibodies which bind to epitopes between 87-108 or both 59-80 and 87-108 of a specified amino acid sequence of hTNF; antibodies which do not bind to specified epitopes of hTNF; and antibodies comprising variable regions comprising specific amino acid sequences or comprising polypeptides encoded by specific nucleotide sequences. Also claimed are methods drawn to use of anti-TNF chimeric antibodies comprising an IgG1 constant region.

Teachings of the References Cited

1. Shalaby et al.

The Examiner indicates that Shalaby et al. teach a method of using anti-TNFα antibodies to prevent graft-versus-host disease (GVHD) in mice, and suggest that antibodies to TNFα may be a useful adjuvant for the treatment of GVHD in humans. Shalaby et al. disclose the results of experiments designed to determine whether rabbit or hamster anti-recombinant murine TNFα antibodies would influence the development of graft-versus-host reaction (GVHR, the acute phase of GVHD in mice) in newborn BDF_1 mice injected with adult B6 spleen cells. (p. 1058, col. 1). The results of the experiments indicated that the inoculations with the rabbit and hamster antibodies reduced spleen enlargement in the test mice.

2. Brennan et al.

The Examiner states that Brennan et al. teach a method of using anti-TNFα antibodies to prevent IL-1 production in mononuclear cells from patients with rheumatoid arthritis and suggest that injection of anti-TNFα antibodies locally in a rheumatoid joint may be a useful therapy in severe rheumatoid arthritis.

Brennan et al. teach that in vitro incubation with rabbit anti-TNFα polyclonal antibody serum reduced IL-1 production in synovial cell cultures from rheumatoid arthritis patients, but not in cultures from osteoarthritis patients. They state that the reason for this difference, despite a high TNFα concentration in both diseases, "is not fully understood", but that their results indicate that inhibition of IL-1 activity only occurs with the high initial IL-1 concentration present in the rheumatoid arthritis cultures. (p. 246-247). Significantly, they state that their results may indicate that other molecules

found in rheumatoid arthritis patients, such as immune complexes or other cytokines, may synergise with TNFα and may be involved in IL-1 production. (p. 246) They suggest that TNFα may damage rheumatoid joints directly and indirectly by IL-1 induction and may therefore be a target for therapy in rheumatoid arthritis.

3. Buurman

The Examiner states that Buurman teaches a method of using anti-TNFα antibodies to prevent shock in humans caused by antilymphocyte antibody therapy. Buurman teaches that patients treated for kidney graft rejection with an antilymphocyte antibody showed elevated plasma TNF levels. (col. 6). He also teaches that antilymphocyte antibodies added to cultures of the patients' peripheral blood mononuclear cells (PBMC) induced, in a dose dependent manner, the release of TNF by the cells in vitro. (Id.) Based on this data, he suggested using anti-TNF antibodies to prevent or treat shock resulting from antilymphocyte antibody therapy. (col. 1).

4. Möller et al. and Rathjen et al. References

The Examiner indicates that, in view of the functional similarities between the A2 antibody and Möller's M195 antibody, they would be expected to recognize the same epitope or a closely related epitope. The Examiner also indicates that Rathjen et al. teach antibodies which inhibit biological activities of TNFα, and some of which bind to epitopes in the region of TNFα which contains an epitope recognized by the A2 antibody. Therefore, the Examiner believes that the M195 antibody and some of the Rathjen antibodies would be expected to competitively inhibit binding of the A2 antibody. The Möller and Rathjen references were discussed at length in Applicants' previous Response, which is incorporated herein. Briefly, Möller et al. teach a species specific murine monoclonal antibody, mAb 195, which neutralizes

human TNF in a murine cachexia model where a lethal dose of hTNF was administered. Rathjen et al. describe antibodies which inhibit the binding of TNF to its receptors.

5. Morrison

The Examiner states that Morrison teaches that chimeric antibodies were considered to be superior to rodent antibodies for use in in vivo therapies, and teaches that methods for producing chimeric antibodies were well established in the art at the time the invention was made. Morrison discusses the possibility that chimerizing a murine antibody may decrease its inmmunogenicity, and reports that murine/human chimeric antibodies have been made.

Improper Combination of References

The Examiner believes that it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to chimerize the antibodies of Möller et al. using the method of Morrison for the treatment of GVHD as taught by Shalaby et al. or rheumatoid arthritis as taught by Brennan et al. or antilymphocyte antibody-induced shock as taught by Buurman.

Applicants disagree. Combining the elements of separate references which do not themselves suggest the combination necessary to obtain a claimed invention is improper. ACS Hospital Systems, Inc. v. Montefiore Hospital, 221 U.S.P.Q. 929, 933 (Fed. Cir. 1984). A prima facie case of obviousness is established only if the teachings of the cited art would have suggested the claimed invention to one of ordinary skill in the art with a reasonable degree of certainty of successfully achieving the claimed results. In re Vaeck, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Both the suggestion and the reasonable expectation of success must be found in the prior art, not in the

applicant's disclosure. Id.

One of ordinary skill in the art would not have been able to predict, given the cited references, whether the chimeric anti-TNF antibodies disclosed by Applicants would be effective in methods for use in pathology, or whether the "A2 epitope" or any particular isotype would be particularly beneficial. That is, none of the references, nor their combination, teach the effective treatment of humans with TNF-mediated disease by administration of anti-TNF antibodies. The references only teach in vitro research and studies involving animal models.

In vitro studies do not suggest the clinical protocols or results of effective in vivo administration of anti-TNF antibodies in humans. For example, although Brennan et al. teach that polyclonal anti-TNF antibodies reduced IL-1 production in cell cultures from rheumatoid arthritis patients, they do not teach that this reduction of IL-1 production actually occurs in vivo or that such a phenomenon will be of clinical importance in the patient. Indeed, the inflammatory response in rheumatoid arthritis is complex. It is possible and, indeed, expected that the anti-TNF antibodies would impact the activities of many factors and that the activities of molecules other than TNF would also be involved in IL-1 production.

The reference does not provide sufficient evidence to suggest that a correlation between the presence of anti-TNF antibody and reduced IL-1 production will result in clinical improvement or what that improvement may be. The reference merely speculates that anti-TNF antibodies may be of therapeutic relevance.

Likewise, Buurman only demonstrated that the in vitro addition of monoclonal antilymphocyte antibodies to PBMC cultures from patients experiencing kidney graft rejection induces the release of TNF by the cells. Buurman describes the administration of anti-TNF antibodies with anti-lymphocyte antibodies to treat shock-related conditions arising from the anti-lymphocyte antibody therapy. He does not teach the actual

production or use of any anti-TNF antibody, nor does he discuss the possible effects of treating TNF-mediated disease by administration of anti-TNF agents of any kind, nor does he discuss the possibility of an immunogenic response to an antibody. Therefore, any suggestion in this reference of a method of treatment of TNFα-mediated shock with an anti-TNF antibody is purely speculative. It is noted with interest that the reliance upon this reference appears to contradict the above rejection relying upon Natanson et al.

The in vitro studies by Möller et al. and Rathjen et al. were limited to determining the ability of their anti-TNF antibodies to bind to TNF and to alter its bioactivity. Möller et al. tested the ability of their antibodies to bind to TNF and related cytokines by enzyme immunoassay, and to neutralize TNF's cytotoxic activity. (Cytokine, supra, at 164; U.S. Patent No. 5,231,024, cols. 6-8). Rathjen et al. tested the effects of anti-TNF antibodies on TNF cytotoxicity, epithelial cell receptor binding, tumor regression and procoagulant induction. (WO 91/02078 at pages 18-20).

Thus, none of these preliminary in vitro studies establish that anti-TNF antibody administration would have any effect on TNF-mediated disease in vivo, or the magnitude and duration of the clinical response and possible adverse reactions of that therapy. As discussed below, the role of each cytokine in the inflammation response is complex. Furthermore, these studies do not demonstrate that the administration of such antibodies would be effective in treating humans, or the clinical importance of that activity. None of these references exemplify chimeric antibodies or the efficacy of such a chimeric antibody.

Combining these in vitro studies with the prior art animal model studies would still fail to provide one of skill in the art with the expectation of successfully practicing the claimed methods or what the result would be. The references disclosing animal model studies fail to teach identification of patients who would benefit from treatment or the timing, duration and delivery

of anti-TNF antibodies to humans. It is noted with interest that the Examiner stated on page 3 of the Office Action that the results from animal models cannot be extrapolated to humans. One reason is that there is great variation in the levels of endogenous TNF production and response to exogenous TNF administration among different species; in humans, the level of endogenous TNF production is very low. (Sun et al., J. Clin. Invest., 81:1328-1331, at page 1330, col. 2). A second reason is that animal models do not mimic the actual disease state frequently in view of the complexity of the inflammation response.

Since none of these in vitro and animal model studies suggests to a person of skill in the art a reasonable likelihood of successfully treating a TNF-mediated disease in a human using chimeric anti-TNF antibodies, the combination of these references does not render the claimed invention obvious.

Furthermore, the cited references do not provide sufficient motivation to chimerize an anti-TNF antibody. Although Morrison discusses the possibility that chimerizing a murine antibody may decrease its inmmunogenicity, and reports that murine/human chimeric antibodies have been made, she does not discuss antibodies directed against cytokines. Furthermore, the presence of nonhuman sequences in humanized antibodies indicates that immunogenicity would still be a concern in therapies involving such antibodies. Moreover, although Möller and Rathjen studied the effects of murine antibodies on TNF bioactivity in vitro, neither exemplified a chimeric antibody or demonstrated clinical benefit. Neither reference reported a HAMA-like response nor suggested the manufacture or use of a chimerized antibody to prevent the response in clinical treatment, or that chimerizing the disclosed antibody would sufficiently reduce the HAMA response to be therapeutically advantageous. In fact, most (if not all) chimeric antibodies, similar to murine antibodies, generate an immune response in the administered animal. Thus, the Examiner's assertion that "one of ordinary skill in the art

at the time the invention was made would have been motivated to chimerize the antibodies of Möller et al. to prevent human anti-mouse antibody antibodies (HAMA)" is clearly incorrect. It was unclear, prior to the data presented in this application, that substantial clinical benefit was possible with a chimeric anti-TNF antibody. Thus, the primary references, which teach antibodies distinct from Applicants' antibodies, in combination with Morrison's general teachings regarding chimerized antibodies, do not provide the necessary reasonable expectation of success of Applicants' claimed methods.

Applicants' dependent claims are drawn to methods using cA2 antibodies, antibodies that possess an IgG1 isotype, antibodies that competitively inhibit binding of TNF to cA2, and/or antibodies that bind to at least one epitope included in amino acids between 87-108 or both 59-80 and 87-108 of SEQ ID NO.: 1 of hTNF and/or antibodies that do not bind to other specified epitopes. The antibodies described in these claims are structurally distinct from those in the cited references.

Significantly, the preferred antibodies of the present invention (Claims 113-118, 120 and 122) are characterized by a different isotype than the antibodies taught by Möller and Rathjen. See Specification, page 36, lines 18-24. This distinction is believed to have important consequences for the effects of the antibodies on TNFα-mediated activity. Scallon et al. have reported that the binding of the IgG1 isotype of cA2 to transmembrane TNFα triggered efficient killing of TNFα-expressing cells by both antibody-dependent cellular toxicity and complement-dependent cytotoxicity effector mechanisms. Cytokine 7(3): 251-259 (1995). In contrast, the binding of the IgG4 isotype triggered significantly lower levels of killing (p. 254-55). Transmembrane TNFα appears to have activities similar to those of soluble TNFα. (p. 251). Additionally, transmembrane TNF expressed on activated T cells has been reported to be part of the cell-to-cell contact-dependent signal that induces immunoglobulin production by B cells. Id. Scallon et al.

indicate that these results suggest that the administration of the IgG1 isotype of cA2 may have therapeutic benefit, not only by inhibiting soluble TNFα activity, but also by inducing lysis of cells that express TNFα. (p. 252, col. 2). The ability of an antibody to neutralize soluble TNF and also to bind to TNF's transmembrane form on cells that produce TNF may be advantageous if it triggers lysis of producer cells or repression of TNF secretion. (p. 255, col. 2).

Applicants' cA2 antibody has the antigen binding variable region of A2, an anti-human TNF IgG1 mAb, and a constant region of a human IgG1, kappa immunoglobulin. Specification, page 36, lines 18-24; page 75, lines 18-20. To highlight the significance of the IgG1 isotype to the efficacy of the antibody, Applicants have added Claims 113-118, 120 and 122, which are specifically directed to methods involving administration of antibodies characterized by the IgG1 isotype. In contrast, mAb M195, the antibody taught in the Möller references, is of the IgG3 isotype. Cytokine, at page 163, column 1, Table 1; U.S. Patent No. 5,231,024, col. 2, lines 15-16. In Rathjen et al., the only antibody for which the isotype is disclosed is mAb 32, which is an IgG2 antibody. (Page 24, lines 31-33). Since the Möller and Rathjen references do not teach the IgG1 isotype of Applicants' antibodies, or the desirability or advantages of selecting this isotype, they do not suggest to one of skill in the art that administration of these antibodies would be effective in treating TNF-mediated disease.

Other claims specify preferred binding properties of the antibody and/or preferred antibodies. Specifically, Claims 112 and 119-122 require the use of cA2 or one or more of the cA2 variable regions. There is nothing within these references which would describe or suggest the selection of the particular antibody, A2, for chimerizing or the specific sequences encoding the variable region. As such, these claims are separately patentable over the references. See In re Bell, 26 U.S.P.Q.2d 1529 (Fed. Cir. 1993) and In re Deuel, 34 U.S.P.Q.2d 1210 (Fed.

Cir. 1995).

Thus, neither Möller et al. nor Rathjen et al. teach Applicants' antibody, and a combination with Morrison's general teachings regarding chimerized antibodies does not provide the necessary reasonable expectation of success of performing the claimed methods using the antibodies disclosed by Applicants. Furthermore, neither Shalaby et al. nor Brennan et al. nor Buurman disclose any method of administration of TNFα antibodies, particularly chimeric antibodies, to humans to treat TNFα-mediated disease.

Therefore, the references do not suggest the invention to one of skill in the art. Nor is the reasonable expectation of success present, since one of ordinary skill in the art would not have been able to predict, given the cited references, whether the chimeric anti-TNFα antibodies disclosed by Applicants would be effective in treating TNFα-mediated disease, or that any particular isotype would be particularly beneficial. Thus, a prima facie case of obviousness is not established for Applicants' claimed invention.

Objective Evidence of Nonobviousness

Further, even assuming, arguendo, that a prima facie case of obviousness exists, which it does not, it would be overcome by the objective evidence of nonobviousness. As consistently recognized by the courts, the determination of nonobviousness must include, as relevant evidence, the "secondary considerations" of Graham v. John Deere, 383 U.S. at 17; 148 U.S.P.Q. at 467.

The secondary considerations described in Graham have been accorded significant weight by the Federal Circuit, as described in Glaros v. H.H. Robertson Co.: "The Federal Circuit has... repeatedly emphasized the importance of the inquiry into secondary considerations, such as the commercial success of the invention and the prior failure of others, as the strongest

precaution against judging an invention from the perspective of 20/20 hindsight." 224 U.S.P.Q. 1037, 1038 (N.D. Ill. 1984), aff'd 230 U.S.P.Q. 393 (Fed. Cir. 1986). Further, in Stratoflex, Inc. v. Aeroquip Corp., the Federal Circuit stated:

> [E]vidence rising out of the so-called "secondary considerations" must always when present be considered en route to a determination of obviousness... Indeed, evidence of secondary considerations may often be the most probative and cogent evidence in the record. It may often establish that an invention appearing to have been obvious in light of the prior art was not.

218 U.S.P.Q. 871, 879 (Fed. Cir. 1983).

The secondary considerations set forth in Graham include, but are not limited to, unexpected results of the invention in relation to the prior art, expressions of disbelief by experts, and evidence that the invention has satisfied a long-felt need in the relevant field. The evidence regarding Applicants' invention establishes all of these factors.

As indicated in Exhibits A through D, incorporated herein in their entirety, researchers have performed clinical studies which demonstrate the safety and efficacy of administering the chimeric anti-TNF antibody cA2 to treat a TNF-mediated disease, rheumatoid arthritis (RA). The patients selected for the clinical studies had long-term, severe refractory disease and a history of failed therapy with several standard disease modifying anti-rheumatic drugs (DMARDs). Thus, the experiences of these patients clearly show long-felt and unsolved need for treatment for this potentially devastating disease. The fact that others in the field had tried for years to achieve a result, yet had failed, "is virtually irrefutable evidence that the [invention] would not have been obvious to those skilled in the art when it was invented." Panduit Corp. v. Dennison Mfg. Co., 227 U.S.P.Q. 337, 248-349 (Fed. Cir. 1985). Nonetheless, despite the duration and severity of their illnesses, the patients treated with chimeric anti-TNF antibody (cA2) experienced significant improvements and tolerated the treatments well, even upon multiple administration.

(See e.g., Elliott et al. 1993, supra, at 1685-1688; Elliott et al. 1994, supra, at 1125-1126; Elliott et al. 1995, supra, at 142-144; Maini et al. 1995, supra, at 206-211 (Exhibits A-D)).

The magnitude of these results in the treatment of a TNFα-mediated disease could not have been reasonably predicted from the prior art references. As noted in Exhibit A on page 1688, due to multiple and overlapping effects of cytokines such as IL-1 and TNFα and the fact that cytokines induce production of other cytokines and of themselves, there had been pessimism about whether targeting a single cytokine in vivo would have any beneficial effect. See, e.g., Exhibit E at page 177 ("...the most important question regarding cytokine intervention in rheumatic disease lies not in its technical feasibility but in the likely effect of interfering with only one cytokine within what is undoubtedly a very complex network. It seems highly improbable that a single cytokine holds the key to RA synovitis."); Exhibit F at page 370 ("...the relevance of tumor necrosis factor and the biological outcome of its banishment by a monospecific inhibitor remain in doubt..."); Exhibit F at page 371 ("Unidimensional attacks on aberrant immune pathways might have limited effect on the underlying disease process"). Initial skepticism as to the merits of an invention by experts in the field supports the nonobviousness of this invention. Hughes Tool Co. v. Dresser Industries, Inc., 2 U.S.P.Q.2d 1396, 1402 (Fed. Cir. 1987).

Since the claimed invention has led to unexpected results and clearly satisfies a long felt but unsatisfied need, the secondary considerations preclude a finding of obviousness. Furthermore, the prior art references do not describe or suggest Applicants' methods of treating TNFα-mediated disease in humans by administering chimeric anti-TNF antibodies, do not provide a reasonable expectation of achieving such antibodies having reduced immunogenicity and a therapeutic benefit, and do not reasonably suggest that the unexpected and superior results achieved and described herein were possible. Thus, withdrawal of the rejection is respectfully requested.

Request for Interview

Applicants hereby request an interview with the Examiner before issuance of the next Office Action.

CONCLUSION

It is respectfully submitted that the claims are now in condition for allowance. If the Examiner feels that a telephone conference would be helpful in expediting the prosecution of the application, the Examiner is encouraged to telephone the undersigned at (617) 861-6240.

Respectfully submitted,

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Dated: 3/10/97
Lexington, Massachusetts 02173